Research Involving Persons at Risk for Impaired Decisionmaking

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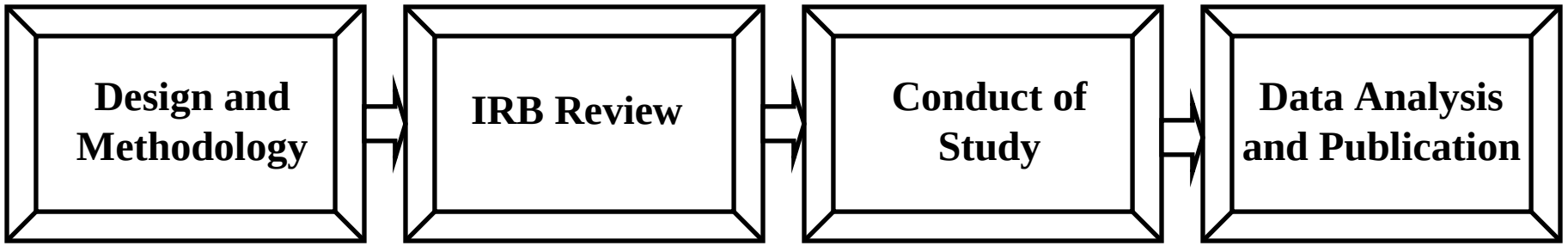
NIMH
National Institute of Mental Health

Overview

- **Non-emergency research with adults**
- **Definitions and overlapping domains**
  - competence
  - cognitive impairment; decisionmaking capacity (DMC)
  - ability to provide informed consent
  - vulnerability
- **Dimensional phenomena and categorical decisions**
- **IRB-oriented perspective; focus on process**
- **Specific additional safeguards**

Research with Decisionally Impaired Subjects



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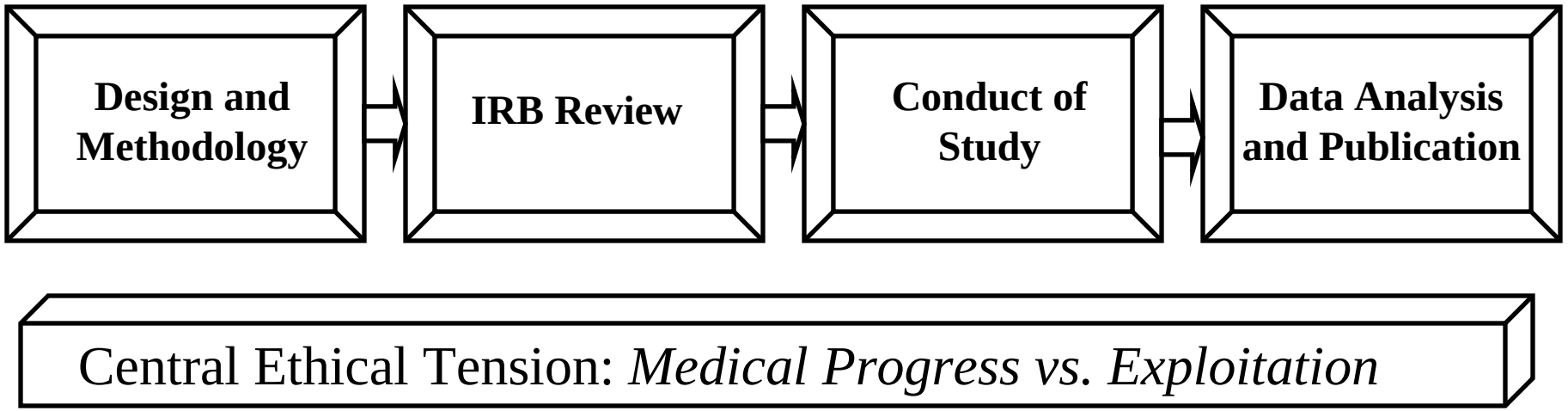

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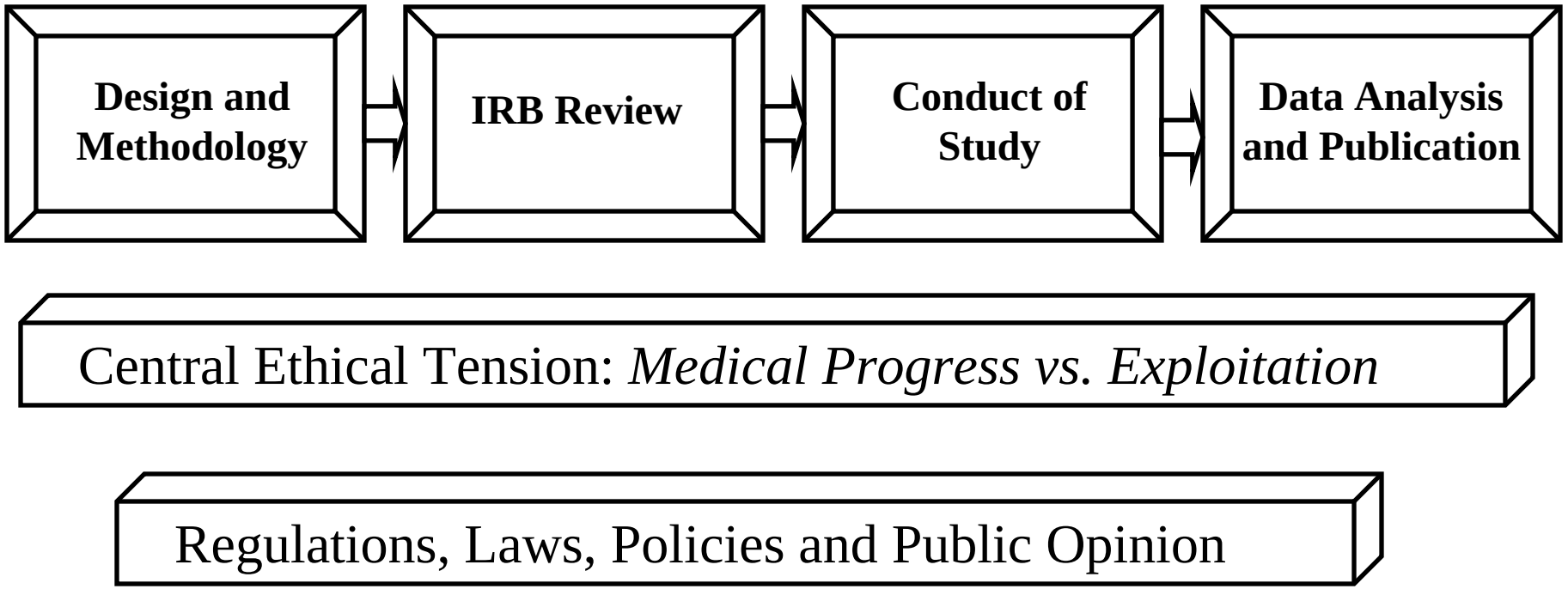

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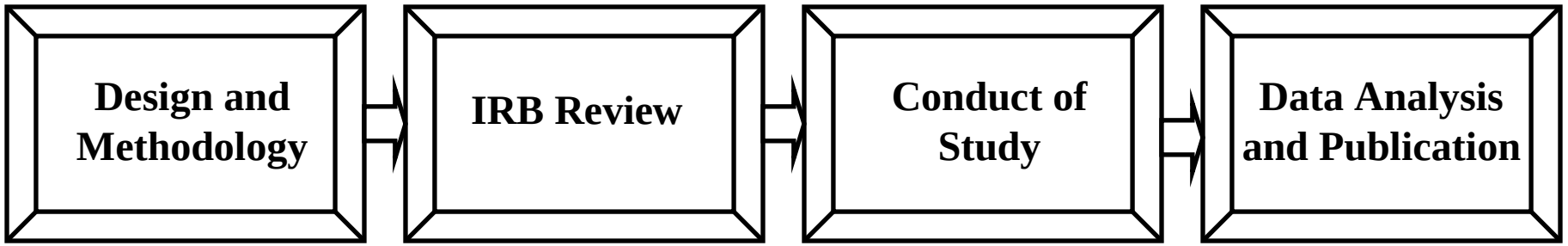

Central Ethical Tension: *Medical Progress vs. Exploitation*

Regulations, Laws, Policies and Public Opinion

(OHRP, FDA, NBAC, MAS 87-4, Advocacy Groups, etc)

Wendler and Prasad, Ann Intern Med, 2001

45 CFR 46.111
Criteria for IRB Approval of Research

(b) When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

Central Questions

1. **Who is vulnerable because of a mental disability?**

2. **What are the appropriate additional safeguards for vulnerable subjects?**

3. **How can these safeguards be optimally implemented ?**

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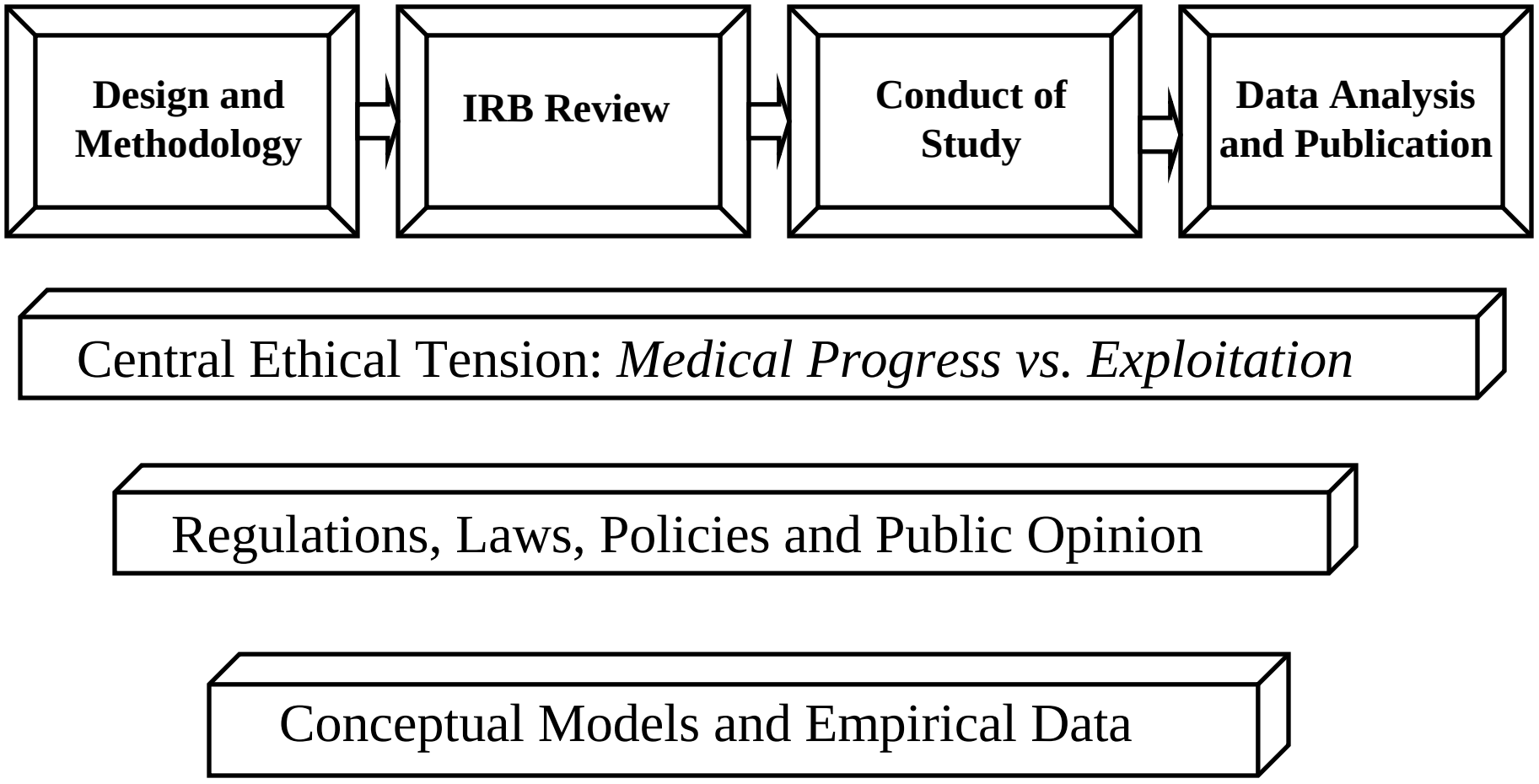


Design and Methodology

- **Subject population**
  - **Subjects unable to provide informed consent**
  - **Early stage and at-risk subjects**
- **Nature of study (medication free, CNS active drug)**

Research With Impaired or Potentially Impaired Subjects

- **Medication trial for Alzheimer's Disease**
- **Comparison of ventilation settings in ARDS**
- **ECT trial for delusional depression**
- **Clinical trial in advanced Parkinson's Dz**
- **Placebo-controlled study in acute mania**
- **Research on delirium**
- **Tryptophan depletion in autism (adults)**
- **Medication-free studies of schizophrenia**

The Most Contentious Case

Research

with subjects who

can not provide informed consent

that offers

no prospect of direct medical benefit

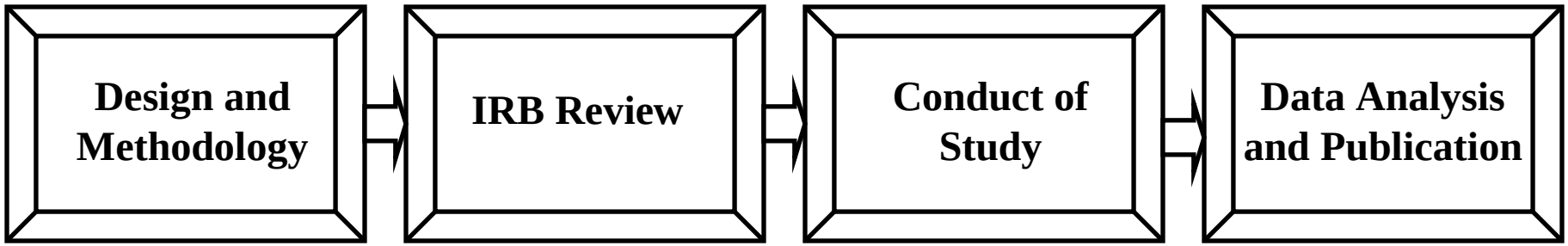
and involves

more than minimal risk

Design and Methodology

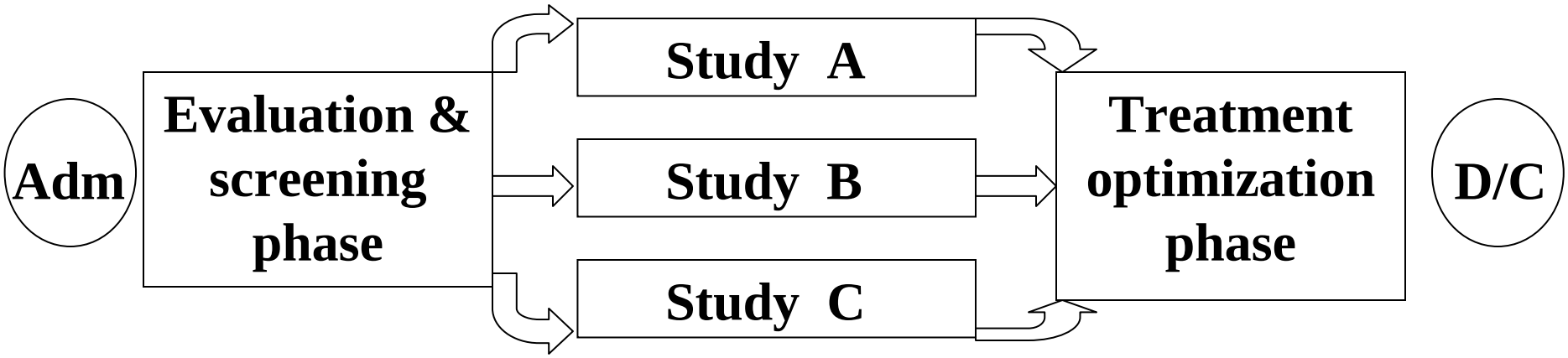
- **Subject population**
  - **Subjects unable to provide informed consent**
  - **Early stage and at-risk subjects**
- **Nature of study (medication free, CNS active drug)**
- **Scientific review**
  - **value**
  - **“necessity” requirement for “non-beneficial” research with subjects unable to provide consent (Wendler et al, IRB 2003)**
  - **feasibility**

Research with Decisionally Impaired Subjects



IRBs review protocols, not programs

Clinical Care in the Context of Clinical Research



clinical Rx	study meds	clinical Rx
data collection (e.g. ratings, scans)		

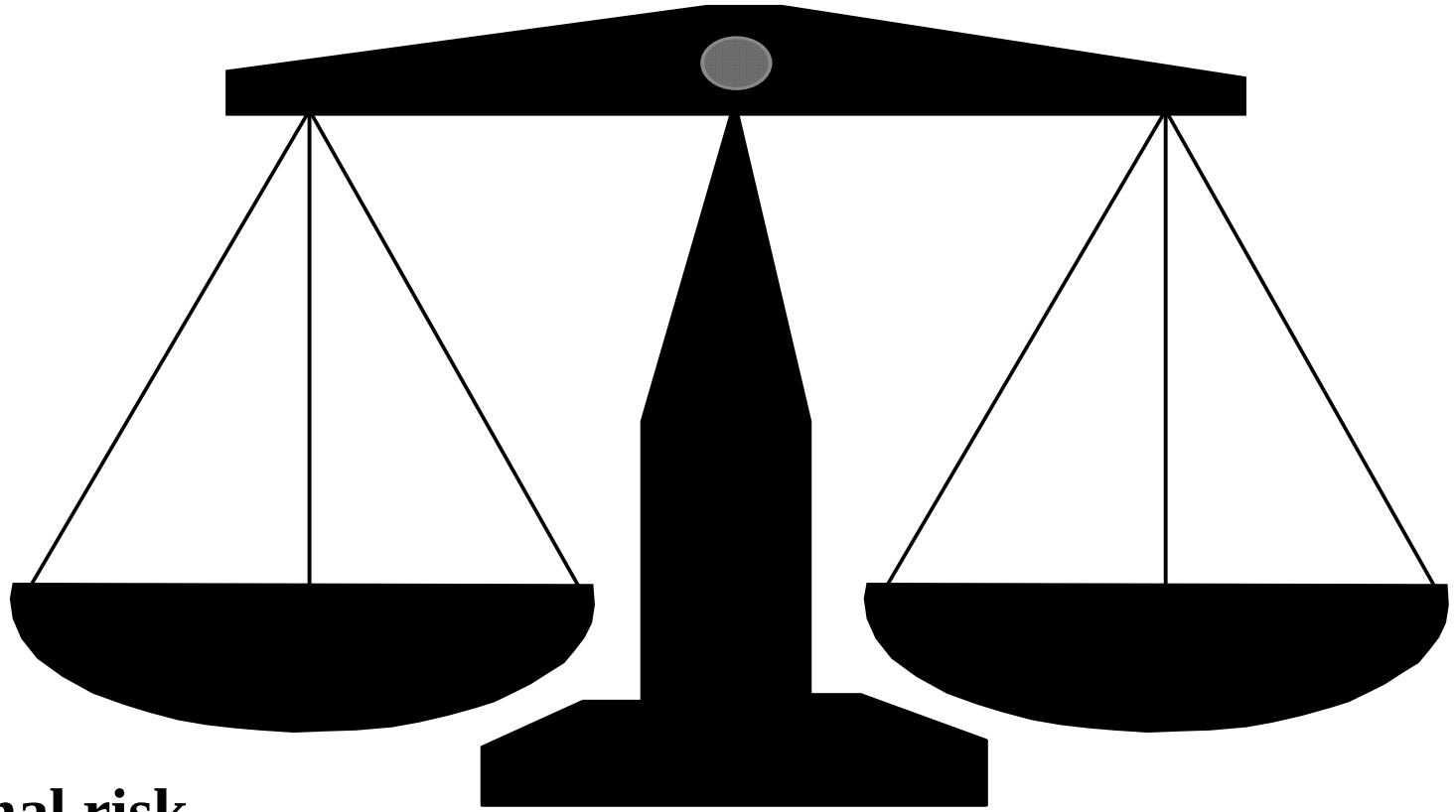
IRB Review

- **Can the scientific question be answered with capacitated subjects?**
  - **Analogy to pediatric research**
  - **Exceptions**
    - **Prospect of benefit**
    - **Prior commitment from subject**
    - **Minimal risk?**

IRB Review

- **Can the scientific question be answered with capacitated subjects?**
- **What are the relevant risks and benefits?**

Institutional Review Board



- **minimal risk**
- **minor increment over minimal risk (children)**
- **greater than minimal risk**

- **direct benefit to the subject**
- **benefit to society**
- **(indirect benefits to subject)**

IRB Review

- **Can the scientific question be answered with capacitated subjects?**
- **What are the relevant risks and benefits?**
- **What is the nature of the anticipated decisionmaking impairment?**

Factors Influencing Decisionmaking Capacity

- **Memory, attention, concentration**
- **Conceptual organization**
- **Psychosis and hallucinations**
- **“Executive” function**

Factors Influencing Decisionmaking Capacity

- Memory, attention, concentration
- Conceptual organization
- Psychosis and hallucinations
- "Executive" function
- Risk assessment
- Mood
- Intuition
- Insight
- Behavior
- Duty and altruism
- "Relatedness"

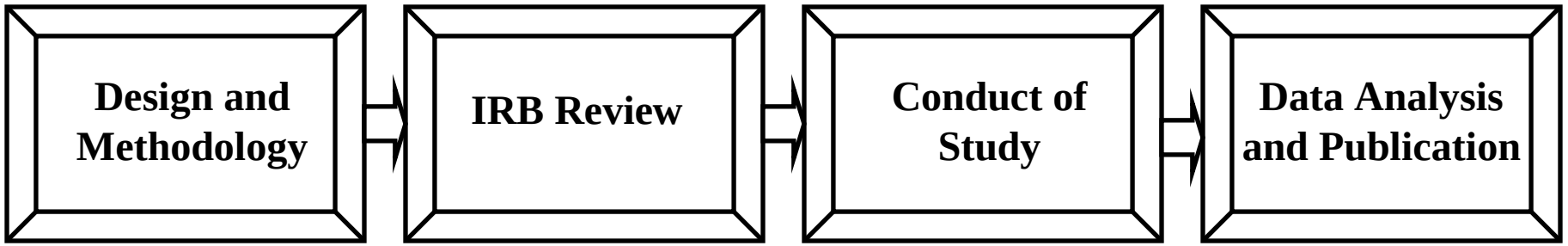
Will Subjects Be Able to Provide Informed Consent?

- **Subjects who are currently unable to provide informed consent**
- **Subjects who will become unable to provide informed consent**
- **Subjects who are at increased risk of becoming unable to provide informed consent**

IRB Review

- **Can the scientific question be answered with capacitated subjects?**
- **What are the relevant risks and benefits?**
- **What is the nature of the anticipated decisionmaking impairment?**
- **Are adequate safeguards in place?**

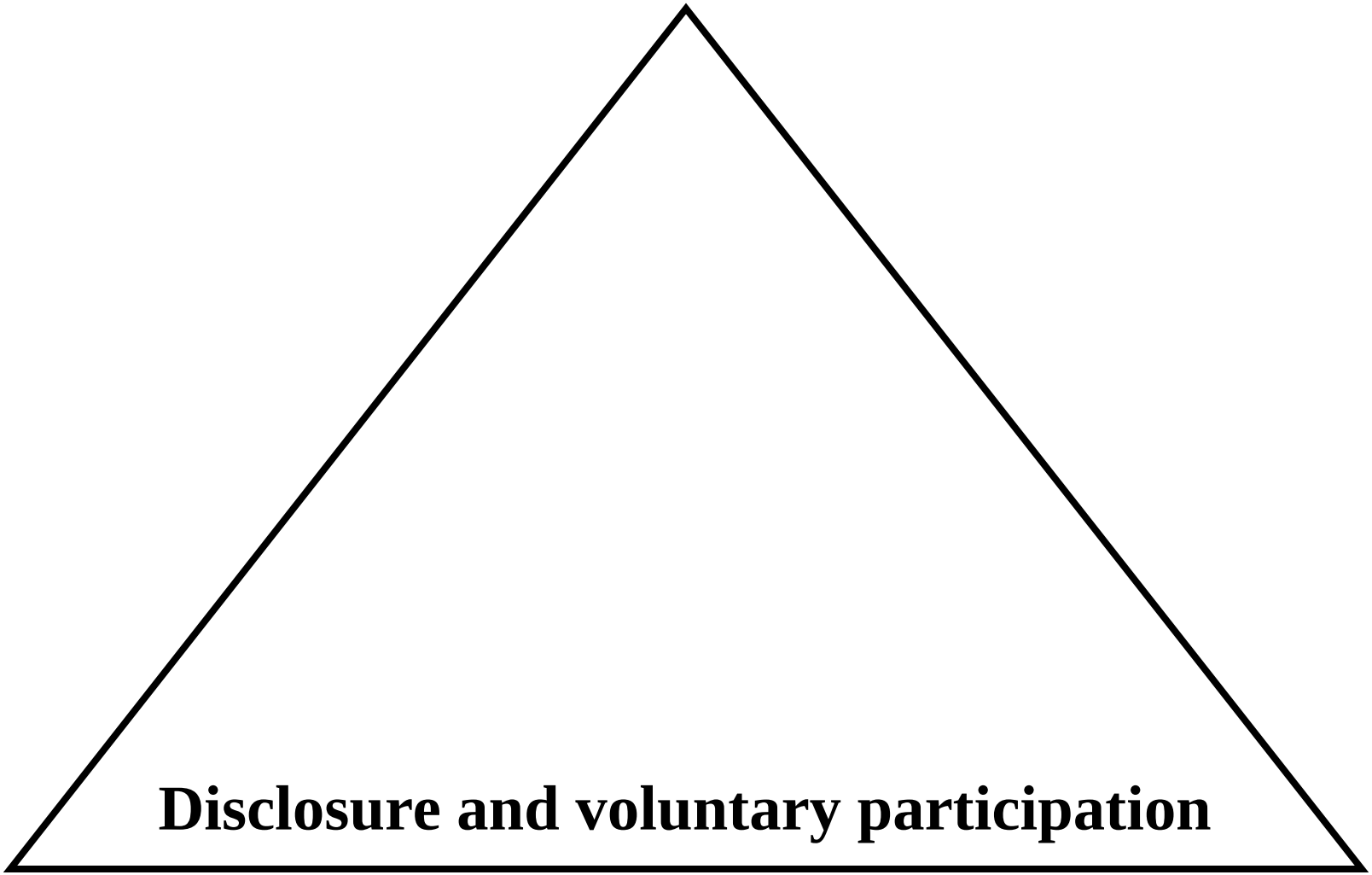
Research with Decisionally Impaired Subjects



Conduct of Study

- **Recruitment**
- **Capacity/consent assessment**

Consent Monitoring and Independent Capacity Assessment



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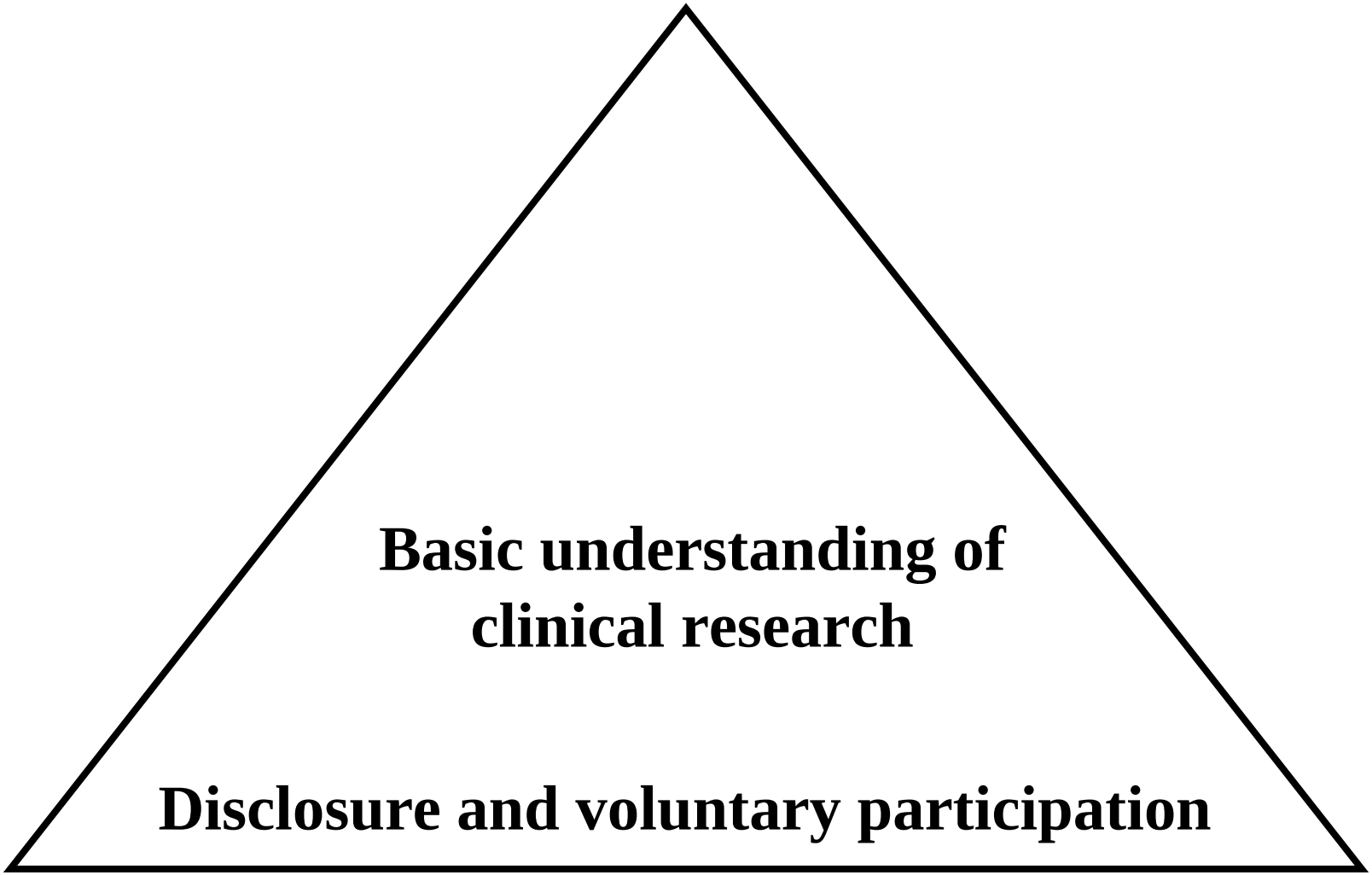

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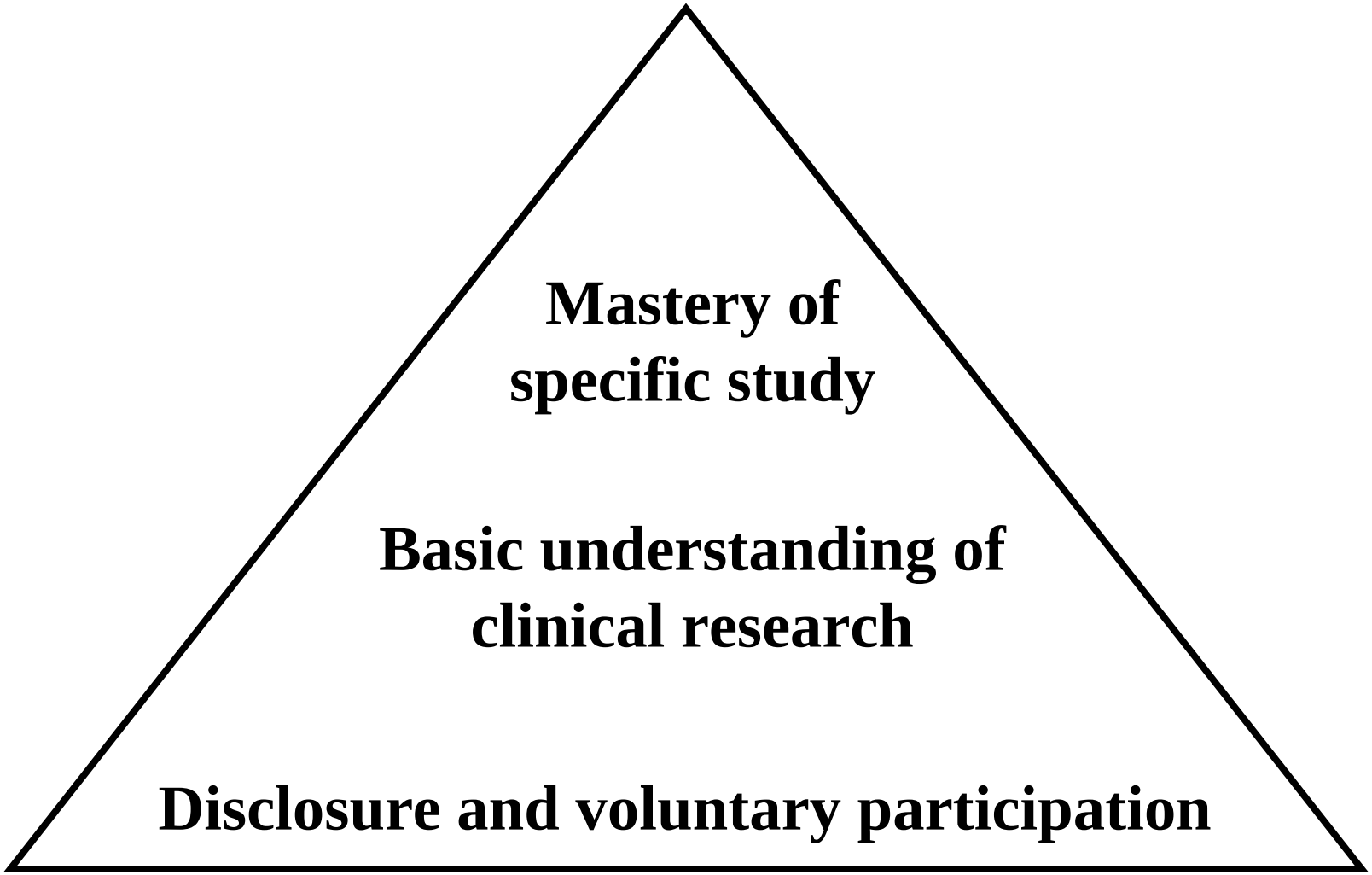
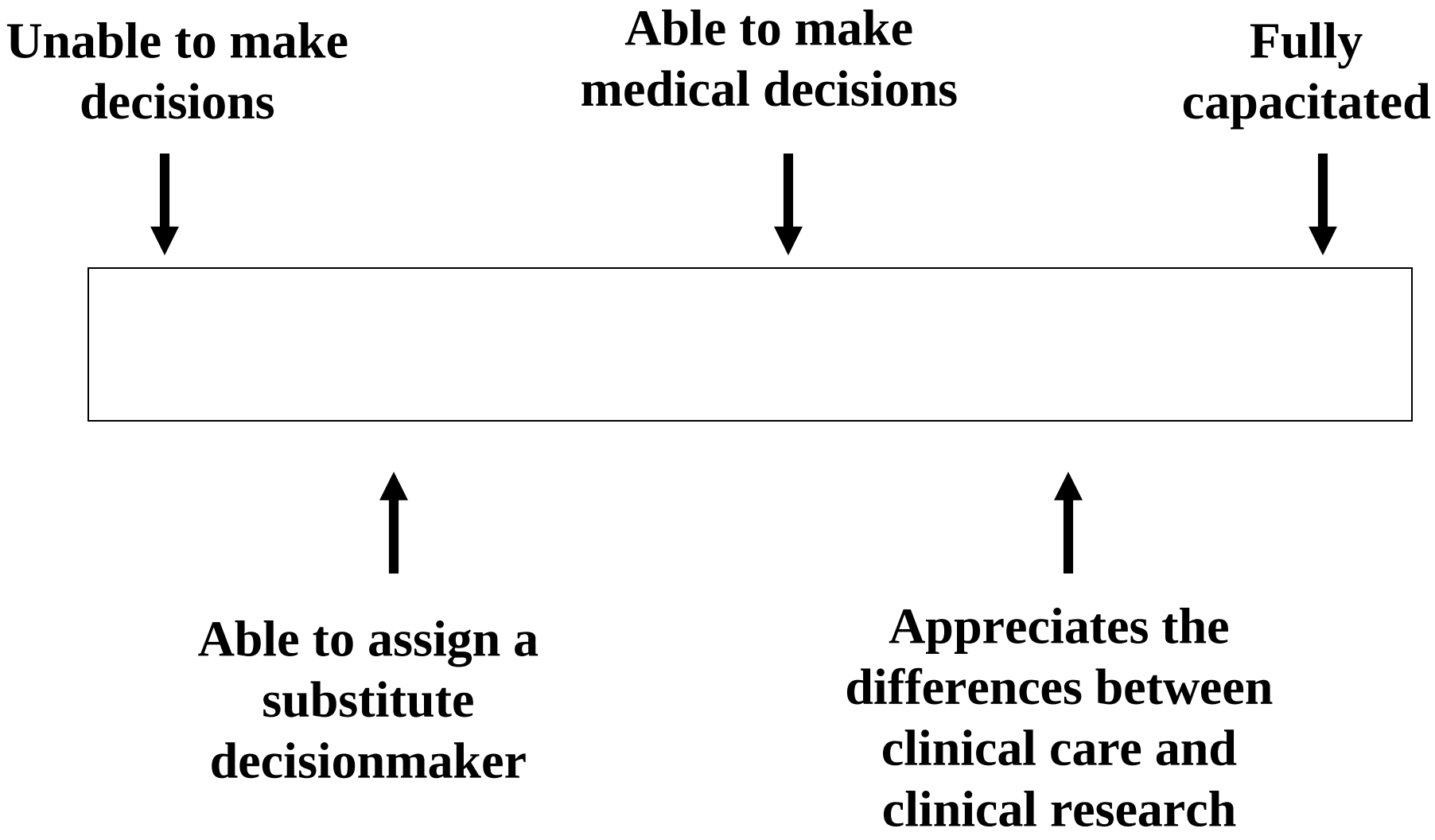


Decisionmaking Capacity



Capacity to Give Informed Consent for Research

Does this individual have a medical, neurological or psychiatric disorder that compromises his or her capacity to understand, appreciate and reason with respect to the details of a given study?

Clinical judgment

Capacity to Give Informed Consent for Research

Does this individual have a medical, neurological or psychiatric disorder that compromises his or her capacity to understand, appreciate and reason with respect to the details of a given study?

Clinical judgment

Can this person give informed consent and should they be enrolled into the study?

Ethical judgment

Triggers for Capacity Assessment

- **Concern about a class of prospective subjects**
  - **Protocol designed to enroll “at-risk” subjects**
  - **Protocol that may precipitate loss of decisional capacity**

Triggers for Capacity Assessment

- **Concern about a class of prospective subjects**
  - **Protocol designed to enroll “at-risk” subjects**
  - **Protocol that may precipitate loss of decisional capacity**
- **Concern about an individual**
  - **Prior to or at the time of enrollment**
  - **During study participation**

Assessment of Decisionmaking Capacity (DMC)

- **Presumption of capacity/competence**
- **Medical aspects of assessment of DMC**
  - **Dehydration, medication toxicity, sickness, delirium, psychosis, severe depression, grief, mania**

Assessment of Decisionmaking Capacity (DMC)

- **Presumption of capacity/competence**
- **Medical aspects of assessment of DMC**
  - **Dehydration, medication toxicity, sickness, delirium, psychosis, severe depression, grief, mania**
- **Who does this?**
- **How is it done?**

MacArthur Competence Assessment Tool (MacCAT-CR)

UNDERSTANDING

purpose of study; what tests and procedures

major risks, discomforts and possible benefits

APPRECIATION

is the main purpose to benefit you?

differences between this study and regular care

REASONING

if you decline, what will you do instead?

whose decision, can you stop participating?

CHOICE

Individuals with Schizophrenia…

- **are at increased risk for impaired decisonmaking abilities**
  - **Carpenter 2000; Grisso and Appelbaum 1995; Moser 2002**
- **are likely to be able to provide IC for a clinical trial**
  - **Carpenter 2000; Moser 2002**
- **can clearly improve ability to provide IC with an educational intervention**
  - **Carpenter 2000, others**

Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Schizophrenia Trial

- **Study of DMC in persons with "moderate" chronic schizophrenia**
  - **57 sites**
  - **1447 subjects**
  - **Inpatients and outpatients with "sub-optimal" antipsychotic treatment**
  - **Randomized to receive typical and atypical antipsychotics**

Lieberman et al; *NEJM* 2005

Stroup et al; *Schizophrenia Research* 2005

CATIE DMC Study (*cont*)

- **Measures obtained at baseline**
  - **McCAT-CR**
  - **Positive and Negative Syndrome Scale (PANSS)**
  - **Neurocognitive battery**
- **Main findings:**
  - **Small inverse correlation between negative sxs and poor performance on three subscale scores of McCAT-CR (positive sxs were not predictive)**
  - **Working memory performance was strongest predictor of all three subscale scores**

Stroup et al; *Schizophrenia Research* 2005

Conduct of Study

- **Recruitment**
- **Capacity/consent assessment**
- **Research authorization**
  - **– informed consent**
  - **– surrogate authorization**

NIH Advance Directive for Health Care and Medical Research Participation

I. Durable Power of Attorney

II. Advance Directive for Health Care

III. Advance Directive for Research Participation

NIH Advance Directive for Health Care and Medical Research Participation

- If I lose the ability to make my own decisions, I do not want to participate in any medical research.
- If I lose…I am willing to participate in medical research that might help me.
- If…won't help me but might help others as long as it involves no more than minimal risk of harm to me.
- If…that won't help me but might help others even if it involves greater than minimal risk of harm to me.

Conduct of Study

- **Recruitment**
- **Capacity/consent assessment**
- **Research authorization**
  - **informed consent**
  - **surrogate authorization**
- **Post-decision questionnaire (PDQ) (Wendler, 2004)**
- **Monitoring of subject status and ongoing consent**
- **Study termination**

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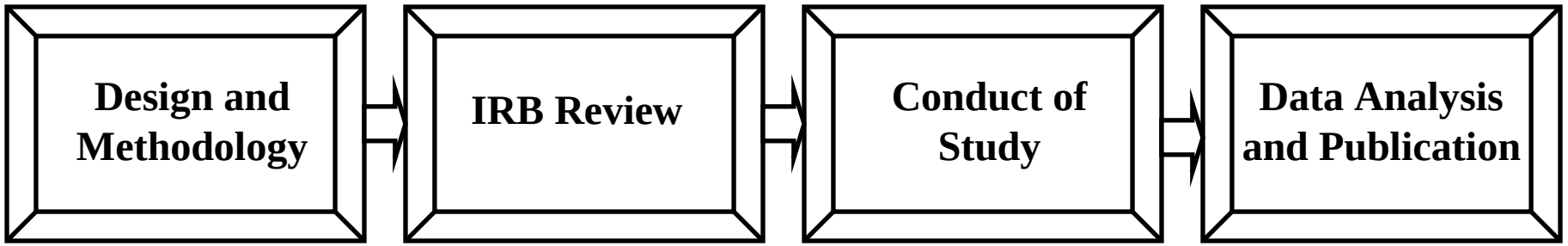

Data Analysis, Publication and Research Feedback to Participants

- Details of methods
- Disclosure of conflicts of interest
- Information-sharing with subjects
  - individual findings
  - aggregate data

Summary and Recommendations

- **Is it necessary to enroll vulnerable subjects?**
- **Decisional capacity with respect to providing informed consent for a specific study**
- **Subject vulnerability, research risks and benefits:**
  - **Determined by local IRB**
  - **Defined by study population and specific protocol rather than by diagnosis alone**

Summary and Recommendations (Cont.)

- **Investigators should describe in detail:**
  - **methods of assessing decisional capacity**
  - **procedures for informed consent or proxy consent**
  - **provision of adequate safeguards**
- **IRBs should promote increased use of:**
  - **independent capacity assessment**
  - **consent monitors**
  - **legally authorized representatives**
  - **research advance directives**
- **IRB discretion regarding intermediate risk**